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SYNTHESIS AND REACTIVITY OF PYRROLO[3,2-E]INDOLE: REMOVAL OF A N-BOM GROUP FROM AN UNACTIVATED INDOLE

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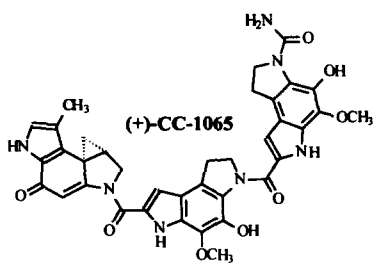
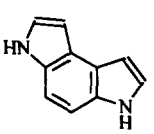
ABSTRACT: A practical synthesis of pyrrolo[3,2-e]indole (**1**) is described. Different hydrogenation conditions of the indol-4-ylacetonitrile (**3**) afforded either 1-BOM-pyrrolo[3,2-e]indole (**4**, 42% from 5-nitroindole) or 1-hydroxymethylpyrrolo[3,2-e]indole (**5**, 46% from 5-nitroindole). Removal of the benzyl group was found to be problematic, but could be accomplished in moderate yield. Treatment of the resulting 1-hydroxymethylpyrrolo[3,2-e]indole (**5**) with NaOH in THF afforded **1** (94% from **5**). Limited studies on the chemistry of **1** are also presented. © 1997 Elsevier Science Ltd. All rights reserved.

The pyrrolo[3,2-e]indole group is the cornerstone of natural product anti-cancer drugs such as CC-1035, and this group of agents has been extensively studied.[2] However, there is a dearth of reports on the synthesis of the parent heterocycle (**1**) in the literature. Cava and co-workers reported the synthesis of a number of C2-substituted pyrrolo[3,2-e]indoles,[3] and Lash and co-workers have detailed a short synthesis of dihydropyrrolo[3,2-e]indoles.[4] However, a report of the parent heterocycle is lacking. Based on the hypothesis that an indole can act as a phenolic bioisostere,[5] we viewed pyrrolo[3,2-e]indole (**1**) as a potential bioisostere of the 5-hydroxyindole component of serotonin. This led us to believe that a synthesis of pyrrolo[3,2-e]indole (**1**) would provide a novel indole template upon which new serotonin agonists could be devised. For these reasons, we sought a simple and efficient route to **1**. In this report, we detail such a synthesis of pyrrolo[3,2-e]indole (**1**), and examine some of the reactivity of this unique symmetrical heterocycle.





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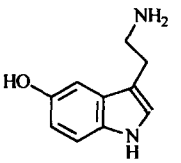


serotonin

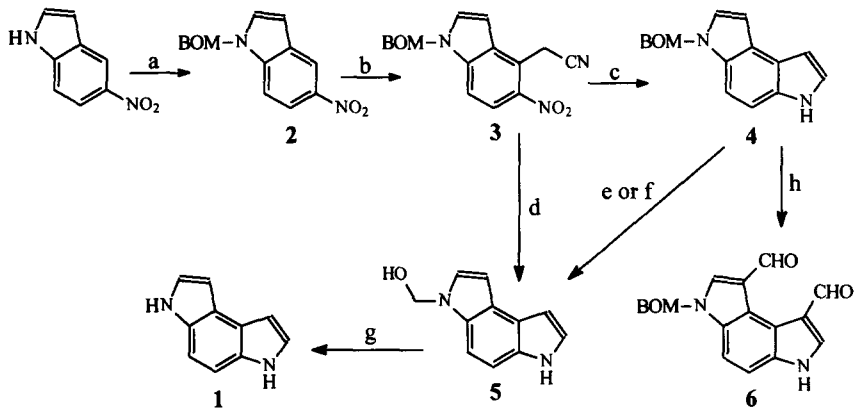
Makosza provided the research framework from which the pyrrolo[3,2-e]indole could be accessed via his previous demonstration that 1-methyl-5-nitroindole participated in a Vicarious Nucleophilic Aromatic Substitution Reaction to provide (1-methyl-5-nitroindol-4-yl)acetonitrile.[6] Other studies showed that (nitrophenyl)acetonitriles could be reductively cyclized to indoles via a palladium catalyzed hydrogenation reaction conducted at elevated temperature.[7] The only factor not available from the literature was the choice of indole N-protection. Previously, Groves and Anderson had used a benzyloxymethyl group (BOM) to protect the indole nitrogen of a 3-ketoindole derivative,[8] but the scarcity of reports following this initial disclosure made us skeptical of the general utility of the BOM group for indole N-protection. However, given the general lack of indole-N protecting groups which are inert to strongly nucleophilic conditions, the BOM group seemed best suited for our purposes.

Reaction of the sodium anion of 5-nitroindole with benzyloxymethyl chloride afforded the protected indole (**2**) in high yield (81%, Scheme 1). Compound **2** participated in a Vicarious Nucleophilic Aromatic Substitution Reaction with *p*-chlorophenoxyacetontrile and potassium *t*-butoxide following the precedent of Makosza[6] to afford the indol-4-ylacetonitrile (**3**, 83%). Reductive cyclization of the indolylacetonitrile (**3**) required precise conditions in order to dictate the exact course of the reaction because some debenzylation accompanied the reductive cyclization of the indolylacetonitrile (**3**). If the reduction was carried out using 10% palladium on carbon (50% w/w) at a temperature slightly above ambient temperature (35 - 45 °C) for 12 hours, a moderate yield (62%) of the BOM-protected pyrrolo[3,2-e]indole (**4**) could be isolated (Scheme 1). In this reaction, 1-hydroxymethylpyrrolo[3,2-e]indole (**5**) could always be seen as a by-product (approximately 10%). If the hydrogenation was carried at 50 - 60 °C for 48 hours, the only product isolated from this reaction was **5** (69%). Therefore, mild hydrogenation conditions allowed for the isolation of BOM-pyrrolo[3,2-e]indole (**4**), while more rigorous hydrogenation conditions afforded the 1-hydroxymethylpyrrolo[3,2-e]indole (**5**, Scheme 1). Accordingly, modifications occurring only on a single pyrrole ring were potentially available with BOM-pyrrolo[3,2-e] indole (**4**), whereas 1-hydroxymethyl-pyrrolo[3,2-e]indole (**5**) was a direct precursor to the symmetrical pyrrolo[3,2-e]indole (**1**, Scheme 1). It should be noted that in neither of these reactions (nor under the conditions described by Groves[8]), was any significant amount of pyrrolo[3,2-e]indole (**1**) seen.

Conversion of **4** to **5** (i.e., discreet reductive removal of the benzyl group) proved problematic. Hydrogenation of **4** at elevated temperature (50-60 °C) over three days using 50% w/w Pd on carbon afforded only a 51% yield of **5** (e in Scheme 1). Crystallization of the residue from the filtrate from the hydrogenation using methylene chloride afforded an easy purification of **5**. In this reaction also, little to no pyrrolo[3,2-e]indole (**1**) was seen. Alternatively, use of ammonium formate as the hydrogen source in refluxing *i*-PrOH with 50% w/w 10% Pd/C effected the conversion of **4** to **5** more rapidly (7 hours), but only a 40% yield of **5** could be obtained (f in Scheme 1). Here again, the ease of crystallization of **5** in methylene chloride greatly aided in its

isolation. Since the hydroxymethylindole (**5**) could be directly obtained from the reductive cyclization of the indolylacetonitrile (**3**), these results suggest that debenzylation may have occurred more readily with **3** than with **4**. The difficulties surrounding the removal of the benzyl group in **4** reflect the fact that few (if any) examples of this type of conversion with a BOM-protected indole can be found in the literature. Accordingly, we are currently trying to optimize this conversion of **4** to **5**.

Scheme 1

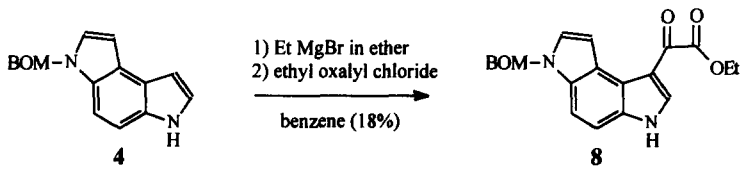


[a] 1) NaH, THF; 2) $PhCH_2OCH_2Cl$ (81%); [b] 4-$ClPhOCH_2CN$, KO*t*-Bu, DMF (83%); [c] 10% Pd/C (50% w/w) , EtOH, 45 °C, 12 h (62%); [d] 10% Pd/C (50% w/w) , EtOH, 60 °C, 52 h (69%); [e] 10% Pd/C (50% w/w) , EtOH, 60 °C, 72 h (51%); [f] 10 eq NH_4CO_2, 10% Pd/C (50% w/w), *i*-PrOH, Δ, 7h, (40%); [g] NaOH (3 eq), H_20/THF (1:9) (94%); [h] 1] $POCl_3$ (2.8 eq), DMF; 2] NaOH, H_20, Δ (68%); [i] $NaBH_4$, THF (87%).

Removal of the hydroxymethyl group in **5** could not be effected under acidic conditions. Under even slightly acidic conditions (i.e., acetic acid in THF), rapid decomposition occurred with no isolation of any identifiable products. Conversely, the hydroxymethyl group in **5** was surprisingly stable to mildly basic conditions. It was found that solid sodium hydroxide in a solution of THF/water was needed to eliminate formaldehyde from **5** forming the symmetrical heterocycle (**1**, 94%).[9] It should be noted that all of reactions shown in Scheme 1 (a - g) have been successfully executed on a greater-than-gram scale. Accordingly, our approach to **1** (a, b, d, and g, Scheme 1) represents an efficient, first synthesis of pyrrolo[3,2-e]indole (**1**).

Simple indolic modifications of the BOM-protected pyrrolo[3,2-e]indole (**4**) proceeded as the literature would suggest. Namely, Vilsmeir-Haack conditions ($POCl_3$ in DMF followed by basic hydrolysis of the resulting iminium intermediate) afforded the dicarboxaldehyde (**6**, 68%, h in Scheme 1). Simple attempts to differentiate the two carbonyls in **6** were unsuccessful. For example, treatment of the dialdehyde (**6**) with sodium borohydride afforded the bishydroxymethylpyrrolo[3,2-e]indole (**7**, 87%). Initial attempts to differentiate the pyrrole moieties in **4** has been troublesome. For example, treatment of the N-magnesium bromide salt of **4** (formed via the reaction of ethyl magnesium bromide and **4**) with ethyl oxalyl chloride afforded only an 18% yield of the desired indole oxalate (**8**, Scheme 2). Significant decomposition of **4** could be seen.

Scheme 2



We are continuing to examine the chemistry of the pyrrolo[3,2-e]indoles (i.e., **1** and **4**), specifically studying methods to efficiently differentiate the individual pyrrolo β-positions (indole C3).

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9) The physical and spectral properties of **1** were as follows: white solid; mp 89.0-92.0 °C; IR (KBr) 3368 (br), 1612, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (br, 2H), 7.23 (s, 2H), 7.20 (t, J=2.8 Hz, 2H), 6.81 (t, J=2.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 130.5, 122.5, 120.1, 106.9, 101.1; LRMS (m/z, relative intensity) 156 (100), 129 (24); HRMS calculated for $C_{10}H_8N_2$ 156.0686, found 156.0688. Anal. calcd. for $C_{10}H_8N_2$: C: 76.90; H, 5.16; N, 17.94. Found: C, 76.74; H, 5.38; N, 17.77.

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